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Discussion: Session 2* Detection of Health Effects of Exposure to Low Doses of Agents—Epidemiologic Problems

Vera Strassman (University of North Carolina) opened the discussion by asking Dr. Radford to comment on methods available for collecting data on subjective and psychological effects arising from conditions in the environment, as part of a total risk assessment in a population. Dr. Radford indicated that there are good psychometric methods for quantitating such effects on individuals, but methods of using these in a population are often difficult. It requires a high order of care in preparation of questionnaires, for example. But the methodology does exist even if it has been applied only in a primitive fashion up to the present time. When we get into the realm of the perception of risk, in many cases public concerns are disproportionate to the actual toxicologic risk. Nevertheless, perceived risks are very important to the people involved. The issue of asbestos in hair dryers is a case in point. He anticipated that this will be an important problem in epidemiology in the coming decade. An example of evaluation of psychosocial impacts is the University of Pittsburgh follow-up study of citizens living around the Three Mile Island nuclear plant, to attempt to assess what the perceptions of the individuals are in that case and how they may relate to health effects or to psychological disturbances.

Jacob Glatter (Environmental scientist, Rockville, Maryland) wanted to know what assumptions, if any, did Dr. Enterline make regarding synergistic effects on risks from asbestos in hair dryers in the home from the active and passive inhalation of carbon monoxide and cadmium that come from lighted tobacco products and, secondly, what assumptions, if any, did he make to take into account any special susceptibility of people living at home, for example with cardiopulmonary disease. Dr. Enterline responded that he did not consider the presence of other contaminants in the home as somehow modifying the effects of the asbestos. He was not sure how to do that, but since he was extrapolating from studies of working populations, those contaminants have probably been present in that environment too. He thought that to extrapolate from occupational environments to general environments, one issue was whether a limit for an 8-hr exposure should be lowered to one-third to apply to a 24-hr/day exposure. With regard to whether exposed groups in the general population may be more or less susceptible than working populations, for cancer he did not think there was much evidence of special susceptibility. For example, the incidence of cancer in the working population is little affected by preselection of the working population. In contrast, working populations have a low incidence of cardiovascular disease compared to the general population.

Dr. Radford asked Dr. Enterline and the panel whether the healthy worker effect applied to cancer as well as to other diseases. Dr. Enterline replied that a problem for industrial studies is: What control populations should be used for comparison? If you compare an occupational population with the general population, and there is pre-

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selection among the workers against a particular disease, that is really an inappropriate comparison. He is convinced that there is not much preselection of workers in terms of who is going to get cancer. There is preselection with regard to who is going to die of cardiovascular disease. The best example is people with rheumatic heart disease, who may not be employed in an industry because they cannot do heavy work. Dr. Radford pointed out that a healthy worker effect does not imply that the only mechanism is by preselection of a specially sensitive population out of the industry. There could be, for example, socioeconomic variables that are quite important. Because an employed group has a steady income, there may be a better diet or better living conditions which can influence subsequent probability of developing disease, including cancer.

Dr. Waxweiler thought the data for cancer are contradictory. For every study where there was not a healthy worker effect for cancer, he thought he could find one where there was. He was not sure why. Perhaps there is selection of susceptibles out of the industry who work a short time and leave employment. For example, Fox found a high lung cancer mortality among vinyl chloride workers who worked for very short times.

Dr. James H. Stebbings, Jr. (University of Minnesota) commented that in Los Alamos, where the County population and the worker population were nearly identical for males, there was a large healthy worker effect among males for GI cancers, but this effect disappeared over about a 30-year period. In contrast, from the very beginning, females showed relatively high rates of GI cancers that males are now beginning to show. These workers were migrants to the region and many were healthy military personnel.

Dr. Schneiderman asked if it was true that no official action was taken by the Consumer Products Safety Commission with respect to banning asbestos in hair dryers. The action that was taken was voluntary on the part of the manufacturers, an example, he thought, of the effect of competitive market forces in dealing with environmental hazards. No matter what the numbers showed, if one manufacturer removed the potentially hazardous material, in this case asbestos, no other manufacturer could afford to say the risk is trivial; the first manufacturer would have a very effective advertising edge, and the second would quickly find his product containing asbestos would lose out in the marketplace.

He also raised the question of computing the dose for materials that may be retained in the body, as opposed to the dose of materials that are ingested and rapidly excreted. If a material is a cancer promoter and is ingested and quickly excreted, it is gone and the promoter action will be minimal. Similarly, if it is a cancer initiator, its action will take place, but might again be reduced because of its short residence time. On the other hand, for materials that stay in the body for long periods of time, initiating and promoting effects continue to take place even at low exposures.

Dr. Enterline replied that Dr. Schneiderman was correct; the action taken was that the biggest manufacturer of hair dryers took the asbestos-containing products off the market, and all the others followed suit. He was referring in his presentation to decision-making, governmental or nongovernmental. Decisions to deal with environmental hazards are made by many people, not necessarily only through government regulations. With regard to the question of retention time of agents like asbestos, it is not correct that inhalation of insoluble materials leads to a progressive buildup. In fact, lung clearance mechanisms are really remarkable. Only a very small fraction of asbestos actually inhaled is retained. Much of it goes back out in the expired air. He did not see that such considerations made any difference in his calculations because he was extrapolating from another environment where asbestos was higher in concentration, but where it may well be that the proportion retained would be approximately the same as for a lower exposure in the inspired air.

Dr. Radford commented that an artifact that has crept into the epidemiology of lung cancer is the alleged synergistic action between cigarette smoking and exposure to asbestos or radon daughters. The evidence that he saw emerging, at least as far as radon daughters are concerned, was that the effect of cigarette smoking is perhaps only slightly more than additive to that of these agents. He believes that the so-called synergistic or multiplicative effect of smoking is an artifact of incomplete follow-up addressed by Dr. Schneiderman. Cigarette smoking apparently shortens the latent period to onset of lung cancer arising from radon or asbestos. In a study with limited follow-up, the cases in smokers develop in considerable excess over those in nonsmokers, but if one is able to study the population for their lifetime, then the excess risk in nonsmokers would approach that of smokers. Cigarette smoking is a much less important factor than has hitherto been thought in terms of the lung cancer risk from exposure to these agents.

Dr. Waxweiler stated that Selikoff's recent data suggest that the relative risk for lung cancer among asbestos workers who smoke cigarettes

compared to nonasbestos workers who smoke cigarettes is about 5-fold. This same relative risk occurs when nonsmoking asbestos workers are compared with nonsmoking, nonasbestos workers. Dr. Radford replied that Selikoff's studies of asbestos workers still showed the effects of follow-up time. Until he has really observed all of the cases that are going to occur over the lifetime of the nonsmokers, their risk will be considerably underestimated. In a study he has currently underway of Swedish iron miners exposed to radon daughters, with good smoking data and almost a lifetime follow-up on all of the cohorts, the relative risk among the smokers is substantially higher than among the nonsmokers, which is what you would predict if the two effects were nearly additive.

Dr. Schneiderman raised the question that an appropriate measure of a combined effect may not be incidence of disease, but years of life lost. If cigarette smoking in asbestos workers or miners results in lung cancer appearing earlier, that is, cigarette products are acting as promoters, then smoking is associated with greater life-shortening. In that sense, the result would correspond to a synergistic effect. After all, the final probability of dying is unity. The issue is the measure used to indicate total risk, not just whether a biological synergism exists or not.

Dr. Radford followed up on a point made in his paper by Dr. Waxweiler, who had brought up the possibility that other materials present in underground mines may interact with radon daughters to raise the lung cancer risk. He believed the evidence was quite strong that other trace contaminants in the environment, whether diesel exhaust, nickel, arsenic or a variety of other agents, are not important. The reason is that there are now several studies in mines with very different minerals and mining conditions. These studies are giving very similar quantitative results, in terms of lung cancer risk to exposure from radon daughters, the one exception being U.S. uranium miners, for whom substantially lower risks have been observed. A radiobiological reason for this difference was available; he thought it had nothing to do with the presence or absence of cocarcinogens. He asked for comment on the extent to which replication of quantitative estimates of risk can be a method of getting at interaction effects from multiple exposure conditions.

Dr. Waxweiler replied that one of Hill's criteria of cause and effect was replication of a finding in a totally different setting. He thought that is one of the most important strengths of epidemiologic evidence. With regard to the studies of miners, it is now possible to look back with hindsight and say that excess lung cancer risk is present for iron, lead and fluorspar miners as well as for uranium miners. It is obvious now that with animal data showing good dose-response relationships for radon daughters, that the risk is primarily from radon daughters and not other trace contaminants, but this conclusion was not obvious at one time. He thought that if one could look at other types of exposures, particularly in chemical plants or among pesticide applicators, synergistic effects or multiple exposures may well be observed and lead to many new hypotheses.

Dr. Sashi Desai (Maryland Department of Health and Mental Hygiene) asked the panel's opinion of a reasonably safe level in the home or in schools of materials such as asbestos or formaldehyde. There are thousands of homes with polyurethane and formaldehyde present. The layman wants to know whether he should rip out that insulation. It is difficult to answer those questions.

Dr. Enterline said he could not answer the question about formaldehyde, but he had mentioned there are cities where the background level of asbestos is about 50 ng/m^3, which is about 25 times the concentration you would get if you sat in a small room with a hair dryer and dried your hair every day. The question is, is there anything happening as a result of this urban exposure? He had estimated 50 cases per million exposed in large cities would get cancer from urban exposure, but there is no way to verify that estimate. Obviously the hair dryer risk is insignificant in comparison.

Dr. Yves Alarie (University of Pittsburgh) said he could appreciate the questioner's concern about hazards from urea-formaldehyde, not only for insulation but also for glueing particle board. He pointed out that these materials were now all over the place. Urea-formaldehyde foam has been banned in Massachusetts and Oregon, and California has a moratorium on it. What had happened is that there had been a misapplication of the product. Urea-formaldehyde is a good product if you apply it properly, but in many instances it was applied during very cold weather. In this case, the two components did not react to completion. Therefore, you have the potential for release of free formaldehyde, and on a hot, humid day free formaldehyde may come into the air. The threshold limit value of formaldehyde is currently 2 ppm. If you would fill this auditorium with 2 ppm of formaldehyde, everyone would complain. Yet, if you go to any of the industries, the workers are working at 2 ppm of formaldehyde and have very few complaints of eye, nose and throat irritation. If one of us walks into that industry, he will complain but, if he stays there for an hour or two,

he would adapt. The problem is some workers and some persons do not adapt, so limits in the home have to be much lower than 2 ppm. To establish safe levels for these people he suggested that the worker exposure limit should be divided by 30 to get a general exposure limit. That is, sensitive people will not experience irritation below 0.06 ppm. But if some were to become allergic to formaldehyde, there would be those who react to exposures of 0.06 ppm. Also newborn infants do not breathe through their mouths, they breathe through their nose. Because formaldehyde is highly water-soluble, with nose breathing almost 100% can be retained in the nose. Infants exposured to low levels of formaldehyde in homes are now coming down with nose-bleeds. He agreed that a lot can be learned from epidemiologic studies in industrial populations, but to apply that knowledge for controlling exposures in the home required a lot of qualifications.

Dr. Desai said that the use of urea-formaldehyde may reduce heating bills by about 40%. It also has good fire resistance. Considering all of those points, is there enough evidence to say that urea-formaldehyde should be banned? If so, what should be done with the existing insulation?

Dr. Alarie replied that the only effective way to deal with improperly applied urea-formaldehyde is to take it out. There is no other solution. People who have built these materials into their homes, sometimes as a result of government recommendations, are in deep trouble. As for urea-formaldehyde being good in terms of fireproofing, he did not agree. It is the most hydrogen cyanide-releasing polymer investigated in their laboratory, and HCN is extremely toxic.

Dr. Gary Spivey (University of California-Los Angeles) questioned dose-response estimation at the low-exposure end. Since most occupational epidemiologic studies involve workers with fairly long-term exposures, and seldom include workers who have had very short exposures, he asked the panel to comment on the effects of that kind of censoring of data at the low dose levels. What does that do to our ability to estimate dose-response relationships at low doses?

Dr. Waxweiler replied that the reason that is often done is because of economics. It is a lot easier to follow persons exposed over five years than those with short exposures. Scientifically he preferred studying everyone and stratifying the analysis by duration of exposure. If you look at the dynamic cohort of a plant population, plotting everyone who has ever worked at that plant by the length of time they have worked there, you generally get a negative exponential curve. If the investigator eliminates those who worked less than a year or less than five years, a very large percentage of workers may not be included in the study. Selikoff and Seidman's study of people who worked very short periods of time, less than a month in shipyards in World War II, found excess risk of lung cancer, as did Fox's study of short-term vinyl chloride workers.

Dr. Radford agreed with Dr. Waxweiler that this was an important problem. The investigator tries to design his study to be able to pick up low-dose effects. But often the study design is set up to exclude short-term employees. For this reason, at low doses either the numerator or denominator is underestimated and there is uncertainty at the low end of the dose-response curve that perhaps should not have existed.

Dr. Schneiderman summed up with comments about the sociology of working. He was disturbed by the high turnover of people who work for a short time. He believed people are selecting themselves out of jobs they find distasteful. If they find a job distasteful, is that in itself an indicator of a long-term effect? Or if persons who find a job particularly distasteful, are those who for some reason are more likely to show effects some time in the future? Have the most susceptible populations then been removed from examination? His experience is that when workers first come to work in a factory, they get the dirtiest jobs. Thus workers with short duration of employment may have exposures to much higher concentrations than long-term workers. He considered that it was important to look into what it is that leads short-term workers to leave a job, and to see if these factors may include some indicators of long-term effects, that is, whether these are really high-risk people.